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EXAMINER

PENG, BO

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1648

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

DETAILED ACTION

1. This Office Action is in response to the amendment filed march 4, 2009. Claims 1-15, 17, 30 and 33 have been cancelled. New Claims 35-40 have been added.
2. Claims 16, 18-29, 31 32, 34-40 are pending. Claims 18-27, 31, 32 and 34 were withdrawn as nonelected. Claims 16, 28, 29 and 35-40 are examined in this Office action.

Foreign Priority Document

3. Receipt is acknowledged of the certified copy of EP 96870053 filed on April 19, 1996, which has been placed of record in the file. A review of the priority document of EP 96870053.4 shows support for probes and primers of SEQ ID NOs: 75, 76, 94, 105, in Table 1, but not claimed primers SEQ ID NO: 112, 134 and 135. Thus, the priority date of probes and primers of SEQ ID NOs: 75, 76, 94, 105 is deemed to be April 19, 1996, the filing date of EP 96870053.4. The priority date of SEQ ID NO: 112, 134 and 135 remains to be April 21, 1997, the filing date of PCT/EP97/02002.

Claim Objection

4. Claim 38 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 29. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

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5. New Claims 35 and 36 are indefinite. Claims 35 and 36 read on a method comprising optional step (i) and optional step (ii), and then active step (iii) hybridizing the polynucleic acids of step (i) or (ii). According to MPEP 2106[R-6] and 2111.04[R-3], claim language that suggests or makes optional but does not require steps to be performed or does not limit a claim to a particular structure does not limit the scope of a claim or claim limitation. Since both steps (i) and (ii) of Claims 35 and 36 are optional, which are not required to be performed, it is not clear with what “the polynucleic acids” the probe of step (iii) is hybridizing. This objection affects all dependent claims. Appropriate correction is required. It is suggested the claims could be amend by adding a separate step X in Claim 35. For example:

Claim 35. A method for determining the presence or absence of HBV genotype A in a biological sample, comprising:

X providing a biological sample comprising polynucleic acids;

(i) optionally releasing, isolating and/or concentrating the polynucleic acids present in the sample;

(ii) optionally amplifying the HBsAg region, or part thereof, of the HBV gene present in said sample with at least one suitable primer pair;

(iii) hybridizing the polynucleic acids of step X

Claim Rejections - 35 USC § 112, first paragraph

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. **(Prior rejection-withdrawn in part-extended to new claims necessitated by**

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the amendment) The rejection of Claim 29 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement **is withdrawn** in view of the amendment. The rejection of Claim 15 is moot in view of the cancellation of the claim. This rejection **is extended** to new Claims 36 and 39 for the same reasons as set forth in Para 8-15 of the Office action dated September 4, 2009.

In response to Applicant's argument:

8. Applicant asserts that the specification describes probes and primers of 5 to 50 nucleotides in length, one of ordinary skill in the art will appreciate that the applicants were in possession of the claimed invention at the time the application was filed.

9. This argument is not convincing. The new Claims 36 and 39 specifically require said method specially "for determining the presence or absence of HBV genotype A in a biological sample". The undefined probes and primers of 5 to 50 nucleotides in length disclosed in the specification cannot specifically detect a sub-genus of HBV genotype A, but not other HBV genotypes in a sample. As indicated in the previous Office action, HBV viruses are known to have high degree of variability in their genomes. The specification has failed to provide an adequate description which probes and primers of 5 to 50 nucleotides in length can specifically identify HBV genotype-A-specific sequences. Therefore, those of ordinary skill in the art would not consider the applicant to have been in possession of the entire breath of the claimed genus of genotype A-specific probes/primers.

10. **(Prior rejection-withdrawn in part-extended to new claims necessitated by the amendment)** The rejection of Claims 16, 28 and 29 under 35 U.S.C. 112, first

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paragraph, as failing to comply with the scope of enablement requirement **is withdrawn** in view of the amendment. The rejection of Claims 15 and 17 is moot in view of the cancellation of the claims. The rejection **is extended** to the newly amended Claims 16, 28, 29 and 35-40 for the same reasons as set forth in Para 16-19 of the Office action dated September 4, 2009.

In response to Applicant's argument:

11. Applicant asserts that the claims have been revised to define probes and primers of the disclosure. Applicant asserts that one of ordinary skill in the art will be able to make and use the claimed invention, without undue experimentation.

12. This argument is not convincing. First, the scope of Claims 16, 28, 29, 35 and 38 encompasses specifically detecting "the presence or absence of HBV genotype A", but not other HBV genotypes, in a sample using any undefined nucleotide probes of about 5 to 18 nucleotides long that hybridizes specifically to SEQ ID NO 77, 140 or 193.

However, it is within the knowledge of one of ordinary skill in the art that a probe that can hybridize SEQ ID NO 77, 140 or 193 is not necessarily able to "specifically detecting a sub-genus of HBV genotype A, but not other HBV genotypes in a sample". As indicated in the previous Office action, a probe that can hybridize specifically to SEQ ID NO 77, 140 or 193 can also hybridize (mismatch) other un-related sequences of other genotype HBV in a biological sample, especially where the claimed method has no indication of hybridization conditions. While the specification shows that probes of SEQ ID NO:77 and 193 can detect genotype A of HBV, it has not demonstrated that any nucleotide probes of about 5 to 18 nucleotides long can specifically hybrid to genotype A-specific target sequences under any hybridization condition, especially low stringy

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condition. Thus, in view of the limited teachings of the present application, the teachings in the art indicating uncertainty in the operation of the claimed method, the alleged method does not enable for determining "the presence or absence of HBV genotype A in a biological sample". One of ordinary skill in the art cannot use the invention commensurate in scope with these claims. Note: This ground rejection could be overcome if claim 35 is amended as following:

"... with at least one nucleotide probe selected from the group consisting of a sequence of 5-17 nucleotides long of which hybridizes specifically to SEQ ID NO 77, a sequence of 5-19 nucleotides long of which hybridizes specifically to SEQ ID NO 140, and a sequence of 5-18 nucleotides long of which hybridizes specifically to SEQ ID NO 193;..."

13. Furthermore, the scope of new Claim 36 encompasses use of any undefined nucleotide probes of about 5 to 50 nucleotides long to specifically detect "the presence or absence of HBV genotype A", but not other HBV genotypes, in a sample. However, the newly cited primers SEQ ID NOs: 75, 76, 94, 105, 112, 134 and 135 appear to overlap with HBV genomes of other genotypes see Specification, Fig. 1. Thus, the cited primers are not genotype-specific. Since the newly cited primers in Claim 36 cannot yield the required result of "determining the presence or absence of HBV genotype A in a biological sample" cited in the preamble of Claim 36, one of ordinary skill in the art will NOT be able to make and use the claimed invention, without undue experimentation.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or

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described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

15. **(Prior rejection-withdrawn)** The rejection of Claims 16 and 29 under 35 U.S.C. 103(a) as being obvious over Maertens (WO 94/12670), in view of Okamoto (J. Gen Virol. 69,2575-2583, 1988) and Norder (J. Gen Virology 73, 1201-12-8, 1992), is withdrawn in view of the amendment to the claims. Applicant's arguments based on prior rejection are moot in view of the new ground(s) of rejection.

16. **(Prior rejection-withdrawn)** The rejection of Claim 28 under 35 U.S.C. 103(a) as being obvious over Maertens, Okamoto and Norder, as applied to Claims 15, 16 and 29 above, and further in view of McDonough (EP0569237A2, 1993), is withdrawn in view of the amendment to the claims. In the prior rejection, Claim 17 was mistaken as Claim 1 because of typography error. The rejection of Claim 17 is moot in view of the cancellation of the claim. Applicant's arguments based on the prior rejection are moot in view of the new ground(s) of rejection.

17. **(New rejection-necessitated by the amendment)** Claims 36 and 39 are rejected under 35 U.S.C. 103(a) as being obvious over Maertens (WO 94/12670), Okamoto (J. Gen Virol. 69, 2575-2583, 1988) and Norder (J. Gen Virology 73, 1201-12-8, 1992).

18. Claims 36 and 39 are directed to a method for determining the presence or absence of HBV genotype A in a biological sample, comprising: (i) optionally releasing,

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isolating and/or concentrating the polynucleic acids present in the sample with at least one of said primer pair consisting of SEQ ID NOs:75, 76, 94, 105, 112, 134 and 135; (ii) optionally amplifying the HBsAg region, or part thereof, of the HBV gene present in said sample with at least one suitable primer pair; (iii) hybridizing the polynucleic acids of step (i) or (ii) with at least one nucleotide probe of about 5 to 50 nucleotides long hybridizing specifically to a HBV genotype A specific target sequence in the HBsAg region of HBV; (iv) detecting the hybrid(s) formed in step (iii); (v) inferring the HBV genotype present in said sample from the hybridization signal(s) obtained in step (iv), wherein step (iii) is a reverse hybridization step.

19. Claim Interpretation: According to MPEP 2106[R-6] and 2111.04[R-3], the language term “optionally” of both steps (i) and (ii) of Claim 36 suggests or makes optional, but does not require steps to be performed, so it does not serve as claim limitation. Thus, both steps (i) and (ii) of Claim 36 do not constitute claim limitation. Claim 36 is interpreted as: A method for determining the presence or absence of HBV genotype A in a biological sample, comprising: ~~(i) optionally releasing, isolating and/or concentrating the polynucleic acids present in the sample with at least one of said primer pair consisting of SEQ ID NOs:75, 76, 94, 105, 112, 134 and 135;~~ (ii) ~~optionally amplifying the HBsAg region, or part thereof, of the HBV gene present in said sample with at least one suitable primer pair;~~ (iii) hybridizing a polynucleic acids present in the sample with at least one nucleotide probe of about 5 to 50 nucleotides long hybridizing specifically to a HBV genotype A specific target sequence in the HBsAg region of HBV; (iv) detecting the hybrid(s) formed in step (iii); (v) inferring the HBV genotype present in said sample from the hybridization signal(s) obtained in step (iv).

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20. Maertens teaches a line probe assay (LiPA) for genotyping viruses, such as HCV, HIV, HBV and/or HTLV present in biological samples (see p. 25). Maertens teaches the method comprises the steps of providing at least one of the probes of HCV and at least one of the probes capable of detecting HIV, or HBV, or HTLV, possibly providing a set of primers to respectively amplify HIV, or HBV or HTLV by means of PCR, contacting the biological sample with the probes under conditions which allow hybridization between the probes and target sequences, see e.g. p. 25 and 26. Maertens specifically indicates that LiPA can be used for determining the type of HBV characterized by incorporating on one and the same strip, probes hybridizing specific to HBV mutants or HBV core, pre-core (see p. 26). Maertens teaches that the probes are immobilized in a line-wise fashion to a membrane strip for reverse hybridization.

21. Maertens does not explicitly teach detecting HBV genotype A specific sequence using a nucleotide probe.

22. Norder teaches the genotype specific sequences of HBV genotype A to F based on the comparison of the complete genomic sequences of 27 HBV strains (whole document, particularly Figure 5, p. 499). The genotype A HBV adw2, pBV933, shown in Fig. 5, has nucleic acid sequence 100% identical to SEQ ID NO: 280 of the specification. (The sequence alignment provided in the previous Office action). Norder specifically points out the different amino acids in each genotype, see e.g. Figure 5 and Paragraphs 496 and 497; and also in *Discussion*).

23. Okamoto teaches 18 HBV strains, which are classified as genotype A to D, wherein genotype A HBV clone 2, pHBV933, has a nucleic acid sequence 100% identical to the genotype A HBV SEQ ID NO: 280 of the specification.

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24. It would have been obvious to one of ordinary skill in the art to modify Maertens' method to detect the presence of HBV genotype A in a biological sample using a genotype-specific probe designed based on known HBV genotype A sequence taught by Norder and Okamoto. One would have been motivated to do so given the knowledge that line probe assay can be used to genotype HBV, as taught by Maertens. There would have been a reasonable expectation of success given the knowledge of HBV genomes of different genotypes as taught by Norder and Okamoto. Maertens's method of detecting specific viral nucleic acids using hybridization probes has general applicability. Because a nucleotide is a nucleotide, no matter what virus produced it, it will hybridize to complementary sequence of a probe. Since both Norder and Okamoto provide nucleic acid sequences of HBV genotypes, it is within the ability of one of ordinary skill in the art to select specific probes from known HBV sequences of different genotypes to determine genotype A-specific sequences. Primer/probe design is a routine practice for one of skill in biological laboratories, as illustrated by Maertens. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Remarks

25. No claim is allowed. HBV genotype A specific target sequences consisting of SEQ ID NO: 77, 140 and 193 are free of the prior art.

26. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37

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CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bo Peng, Ph.D. whose telephone number is 571-272-5542. The examiner can normally be reached on Tu-F, 8:30-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/BO PENG/

Primary Examiner, Art Unit 1648